# EXHIBIT D

Lions Eye Institute

# 2012 ANNUAL REPORT

A clear vision to the future

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# molecular ophthalmology

**In January, 2012, the Human Gene Therapy Trial started on a very select group of patients. The trial is a culmination of 15 years of work by the Molecular Ophthalmology team to develop a new treatment for wet age-related macular degeneration.**

## OUR OBJECTIVES ARE TO:

- Understand the pathomechanism of wet-AMD
- Develop animal models for the disease
- Develop long term treatment strategies for wet-AMD - gene therapy
- Produce the appropriate viral constructs
- Test the viral constructs *in vitro* (cell cultures), *in vivo* (mouse model) and in pre-clinical settings (monkey model)
- Conduct Phase I and II human trials.

## PROJECTS AND OUTCOMES

### Recombinant adenoassociated virus mediated gene therapy trial

In 2012, chief clinical investigator Professor Ian Constable recruited 20 patients for the trial with the able assistance of trial coordinator Cora Pierce. The excellent work of Assoc Prof May Lai and Dr Aaron Magno ensured Molecular Ophthalmology's research practices were converted into an auditable laboratory service suitable for the analysis of thousands of samples with complicated molecular assays. The safety data of the first eight patients was reported at the meeting of the American Society for Cell and Gene Therapy in May 2012. To date, all patients are doing well and we are looking forward to further data analysis in 2013.

### Complications of Lucentis Therapy

We have successfully developed an assay for the detection of Lucentis antibodies in patients undergoing Lucentis therapy and tested the first 40 patient samples.

### Diabetic Retinopathy - Development and characterisation of animal models

In previous years, we successfully developed a mouse model for retinal neovascularisation that can be examined in normal (Kimba) and diabetic (Akimba) animals. These models were met with an enthusiastic world-wide response and further licenses have been granted to Monash University, Melbourne University, Cornell University in the USA, Kyushu University in Japan and KOWA Company Ltd.

In collaboration with Professor Paul McMenamin, we also continued our studies on the Akita mice and characterised several new features of the model. Unfortunately, we could not confirm initial reports by other groups about the suitability of this model for studying diabetic retinopathy.

### Retinitis Pigmentosa

Although more than 130 genes have been associated with retinitis pigmentosa, the most prevalent causes of the disease are mutations occurring in the gene that codes for rhodopsin.

Following a previous study that demonstrated a correlation between rhodopsin stability and the severity of retinitis pigmentosa, we investigated whether predictions of severity can be improved by a regional analysis of this correlation.

We developed a new cell-based procedure to measure an important cell biological marker - the amount of rhodopsin on the cell surface - and showed a correlation between the stability of rhodopsin mutations and disease severity.

This type of high throughput measurement and computer based stability calculations could improve prognoses for poorly characterized mutations and provide a platform to measure the effectiveness of treatments in the future.

## GRANTS/FUNDING

- NHMRC Project grant - Long-term human response following subretinal injection of recombinant adenoassocited virus-sFlt-1 vector
- NHMRC Project Grant - Do resident immune cells cause retinal damage in diabetes?
- Richard Pearce Bequest
- Avalanche Biotechnologies, USA